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EXAMINER
SCHWADRON, R

PATREA L. PABST
KILPATRICK & CODY
1100 PEACHTREE ST., SUITE 2800
ATLANTA, GA 30309-4530

18M1

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-17 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-17 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

15. ~~formal~~ Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

16. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-17 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed invention for inhibiting microvascular bleed as therapeutic in human patients. Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has not effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. Waldmann teaches that effective therapy using monoclonal antibodies in the

therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by in vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Therefore it does not appear that the asserted utility of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01(p) .

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present a best mode of carrying out the invention.

A) Applicant has not disclosed how to use an anti protein C antibody or inhibitor of a natural anti coagulant therapeutically in humans. There is insufficient written description of the

invention with respect to the in vivo operability in humans of an anti protein C antibody or inhibitor of a natural anticoagulant to use applicants invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 17). Therefore, it would require undue experimentation of one of ordinary skill in the art to determine how to use the claimed protein for the reasons discussed. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

B) Applicant has not provided evidence that inhibitors of a natural anti coagulant other than anti protein C antibodies will reduce microvascular bleeding. Applicant discloses that examples of such inhibitors are antibodies against Protein S, thrombomodulin, antithrombin III, heparin cofactor II and tissue factor inhibitor(s), as well as specific chemical inhibitors (page 13, lines 13-16). There is insufficient written description of the invention with respect to the in vivo operability of the aforementioned inhibitors of a natural anti coagulant. Therefore, it would require undue experimentation of one of ordinary skill in the art to determine how to use the claimed protein for the reasons discussed. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

C) The specification lacks complete deposit information for the cell line HPC-4. Because it is not clear the cell line called HPC-4 is known and publicly available or can be

reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of monoclonal antibodies produced by this hybridoma a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the instant invention or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell lines is an unpredictable event. Note that the best mode is not satisfied by a written disclosure unless the exact embodiment is reasonably reproducible from that disclosure. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the cell lines will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR § 1.801-1.809, Applicant may provide

assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) During the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) All restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) The deposits will be maintained in a public depository for a period of 30 years from the date of deposit or for the enforceable life of the patent or for a period of five years after the last request or for the effective life of the patent, whichever is longer;

(d) The deposits were viable at the time of deposit; and;

(e) The deposits will be replaced if they should ever become non-viable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and street address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the cell lines producing the HPC-4 antibodies described in

the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2. 1216, 227 USPQ 90 (CAFC 1985), for further information concerning deposit practice.

18. Claims 1-17 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

19. Claims 1-17 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a method of reducing microvascular bleeding at the site of skin graft removal in domestic swine treated with anti protein C antibody, or the combination of anti protein C antibody and topical administration of thrombin or tissue thromboplastin. The specification is not enabling for treating humans with any anti protein C antibody or anti natural coagulant, alone or in combination with topical administration of thrombin or tissue thromboplastin. The enablement is not commensurate with the scope of the claims that microvasular bleeding in humans can be treated with anti protein C antibody or anti natural anticoagulant, alone or in combination with topical thrombin or tissue thromboplastin. See M.P.E.P. §§ 706.03(n) and 706.03(z).

20. Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 14 are indefinite in the recitation of "inhibitor of a natural anticoagulant" because it is not clear what this encompasses. Claims 1 and 14 are indefinite in the recitation of "tissue factor inhibitor pathway" because it is unclear what this means. Claim 5 is indefinite because the treatment lacks antecedent basis in claim 1. Claim 8 is indefinite in that "in combination with topical administration of a coagulant at the site of bleeding" lacks antecedent basis in claim 1. Claims 6 and 9 are indefinite in that they are dependent on inappropriate claims 5 and 8, respectively. Claim 17 is rejected as being a duplicate of claim 16 (See MPEP 706.03(k).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

22. Claims 1-4,7,10,15 rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Esmon et al. (US patent 5,147,638).

Esmon et al. teach inhibition of microvascular bleeding by treatment with anti-protein c antibody (see column 14, paragraph

2).

23. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

24. Claims 5,6,8,9,11-13,14,16,17 are rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,147,638) in view of Suzuki et al. The claims are drawn to a method of inhibition of microvascular bleeding by treatment with an antibody against an anticoagulant and a coagulant.

The claims of the instant invention are also drawn to treatment for burn patients, tissue or skin grafts or cerebral contusions. Esmon et al. teach inhibition of microvascular bleeding by treatment with anti protein c antibodies (an antibody against an anticoagulant, see column 14, paragraph 2). Esmon et al. does not teach the use of the coagulant thrombin in addition to antibodies against protein C or the use of this combination to treat the aforementioned clinical conditions.

Suzuki et al. (page 271, first paragraph) teach the use of thrombin as a coagulant, when administered systemically or topically for the treatment of injured skin (burn patients or skin grafts) and injured organs (tissue grafts or cerebral contusions). It would have been prima facie obvious to one of ordinary skill in the art to combine the use of anti protein C antibodies and thrombin where one or both of these coagulation promoting agents are given systemically while also administering thrombin topically because both of these agents can promote clotting and a combination of the two agents could result in greater coagulation. It would have been prima facie obvious to one of ordinary skill in the art to use thrombin and tissue thromboplastin as an alternative to thrombin alone in the instant invention because tissue thromboplastin is simply another coagulant well known to one of skill in the art. One of ordinary skill in the art would be motivated to use the instant invention for the treatment of burn patients, skin or tissue grafts or cerebral contusions as an improved means to inhibit microvascular bleeding ~~with~~ in these conditions. One of ordinary skill in the art would have a reasonable expectation of success of inhibiting microvascular bleeding with a combination of ~~by~~ anti protein C antibodies and a coagulant because Esmon et al. teach inhibition of microvascular bleeding by anti protein C antibodies and Suzuki et al. described thrombin and its use for inciting coagulation in

a variety of clinical conditions.

25. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PRO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron whose telephone number is (703) ~~305~~ 308-4680.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ron Schwadron

Ron Schwadron, Ph.D./sg
February 24,1993/tf

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
2/26/93